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REMARKS

Claims 18-20 are pending in the present application. Claims 18-20 have been withdrawn and new claims 33-82 submitted. No new matter has been introduced by these new claims, antecedent basis therefor being found throughout the specification and claims as filed. Reconsideration and allowance of the claims is respectfully requested in view of the above amendments and the following remarks.

1. Claim Rejections Under 35 U.S.C. § 102

Claim 18 (corresponding to new claims 33, 54 and 73) stands rejected under 35 U.S.C. § 102(b) as being anticipated by Goetzl et al. (Proc. of the Association of American Physicians, May-June 1999,111(3) p259-69) and Goetzl et al (J. of Immunology, Feb. 15, 1999, 162 (4) p2049-56). These references teach the use of plasmids encoding antisense messages for EDG-2, -3, -4 and –5 to reduce the expression of their respective EDG receptor.

The instant disclosure teaches antisense oligonucleotides that are distinctly different from the antisense messenger RNA (mRNA) taught by the Goetzl references. The Goetzl references show that the DNA encoding an antisense mRNA may be used to modulate the expression of EDG receptors. The EDG receptor antisense mRNA is an RNA of length greater than 1000 nucleotides. To one skilled in the molecular biology arts, an oligonucleotide is a short nucleic acid, short being significantly smaller than 1000 nucleotides. The NIH Medical Subject Headings define an oligonucleotide as polymer made

up of a few (2-20) nucleotides. Thus the antisense oligonucleotides of the instant disclosure are different from the antisense mRNAs of the Goetzel references.

Additionally, applicants note the design of an antisense oligonucleotide is very challenging. The A.D. Branch reference (TIBS 23, 45-50, 1998) cited by the Examiner states "The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules." Thus the success of antisense mRNAs in inhibiting gene expression in the Goetzel references does not guarantee the success of antisense oligonucleotides. The antisense mRNA can bind single stranded regions within the whole molecule, while an antisense oligonucleotide is complementary to only a small portion of the mRNA. Applicant respectfully submits that the antisense oligonuclotides of the instant invention are not anticipated by the cited reference. The applicant respectfully requests consideration of the new claims.

2. Claim Rejections Under 35 U.S.C. § 112

Claims 19-20 stand rejected as being indefinite for using the language "one or more of", "analog" and "derivative". Claims 19-20 have been withdrawn. New claims 36-39, 57-60 and 76-77 are presented, which specifically set forth the various analogs and derivatives.

Claim 18 stands rejected as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention".

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The examiner objects to the breadth of the claims to include any possible EDG gene. New claims are directed to EDG-1 and EDG-3.

The examiner further states "the specification, while being enabling for antisense to EDG in cells in culture (in vitro), does not reasonably provide enablement for antisense to EDG for function in cells in whole organisms (in vivo)". The Examiner cites two references that describe the difficulties with the use of antisense compounds in vivo (Flanagan et al. and Branch).

Applicants respectfully traverse the rejection on the basis that the specification does provide enablement for antisense oligonucleotides in vivo. In vivo can mean local administration as well as whole body administration. The effect of the antisense phosphorothioate oligonucleotides in an in vivo model is shown in Example 12, Figure 17 of the application. The model used is the matrigel implant model of subcutaneous angiogenesis in athymic mice. It is shown in Figures 11A and 11B that SPP induces angiogenesis as evidenced by an increase in vascular density and the appearance of mature vascular structures. The data in Figure 17 shows that the antisense oligonucleotides to EDG-1 and EDG-3 attenuate the SPP-induced formation of mature neovessels.

There is precedent for successful local administration of antisense oligonucleotides, similar to that in the mouse model of the instant application. Olson et al. (Clin. Cancer Res. 7(11):3598-605 (2001)) reports that local treatment of a tumor with an antisense oligonucleotide protected mice from developing prostate tumors. It was further shown that systemic administration of the same antisense oligonucleotide prevented lymph node

micrometastases in 47% of mice. This study shows that both local and systemic administration of antisense oligonucleotides are effective anti-cancer therapies.

Further evidence of the in vivo effectiveness of antisense oligonucleotides is the FDA approval of the first antisense drug. Vitravene or formvirsen sodium injectable is approved for local treatment of cytomegalovirus retinitits in AIDS patients.

Applicants submit that the mouse model data, cited paper and FDA approval of an antisense drug support the in vivo use of an EDG receptor antisense oligonucleotide. One skilled in the art of antisense oligonucleotide therapy would be able to use the EDG receptor antisense oligonucleotide to inhibit EDG receptors in vivo without undue experimentation.

It is believed that the foregoing amendments and remarks fully comply with the Office Action and that the claims herein should now be allowable to Applicants. Accordingly, reconsideration and allowance is requested.

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If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130 maintained by Applicants' attorneys.

Respectfully submitted,

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